REMARKS

The allowability of claim 8 is noted if written in independent form. Reconsideration of the rejection of claims 1-3, 5, 6, 9, 10, 12 and 13 is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

For clarity of presentation of the amended claims, the phrase "in vivo" has been replaced in the claims with "*in vivo*", with no change in intended or actual meaning or scope of these claims. Claims 1, 9, 10, 12 and 13 have been amended to more specifically provide that the "*in vivo* cleavable ester" is formed on an available carboxy or hydroxy group of the defined compound, as discussed further below. The above amendments are being made to expedite prosecution of this application to allowance, and are without abandonment or prejudice to applicants' right to prosecute any deleted subject matter of these claims in one or more continuing applications.

New method claims 14-18 have been added based on specification disclosure specifically discussed below.

Following entry of the above amendments, claims 1-3, 5, 6, 8-10 and 12-18 are pending in this application.

Remaining Grounds for Rejection

The only remaining outstanding grounds for rejection, as understood, are:

- The rejection of claims 1-3, 5, 6, 9, 10, 12 and 13 as being indefinite under section 112, 2nd paragraph with respect to the phrase "*in vivo* cleavable ester" recited in claims 1, 6, 10 and 12 (Action at pages 2-3);
- The rejection of claims 1-3, 5, 6, 9, 10, 12 and 13 under section 112, 1st paragraph, "because the specification, while being enabling for making the *in vivo* cleavable esters listed in lines 4-13, page 23, does not reasonably provide enablement for making all *in vivo* cleavable esters" (Action at pages 5-6);
- The rejection of claim 12 as being indefinite under section 112, 2nd paragraph, in that "the claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is 'a disease or medical condition mediated by TNF'" (Action at pages 3-4).
- The rejection of claim 13 as being indefinite under section 112, 2nd paragraph, in that "the claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is 'a disease or medical condition mediated by IL-1, IL-6 or IL-8'" (Action at pages 4-5).
- The rejection of claims 12 and 13 under section 112, 1st paragraph, "because the specification, while being enabling for treating rheumatoid arthritis and psoriasis, does not reasonably provide enablement for treating all TNF, IL-1, IL-6 and IL-8 mediated diseases" (Action at pages 7-10)

Section 112 Rejection Based on the Phrase "in vivo cleavable ester"

Claims 1-3, 5, 6, 9, 10, 12 and 13 have been rejected under section 112, 1st and 2nd paragraphs by reason of the recitation of "*in vivo* cleavable ester" in claims 1, 6, 10 and 12.[1] These section 112, first and second paragraph grounds for rejection do not appear to add anything substantive to the previous rejections, which were exhaustively addressed in applicants' Amendment and Response of November 6, 2002 at pages 8 to 14, and applicants' Amendment and Response after final filed May 30, 2003 at pages 17-19, and are cross-referenced here rather than being repeated.

What is clearly evident from those arguments and cited patents and literature (as well as the guidance of the present specification at pages 22-23) is that a skilled medicinal chemist would be well aware of what is embraced by the concept of prodrugs, and in particular the type of prodrug that is an *in vivo* cleavable ester, and would be quite capable of making *in vivo* cleavable esters based on that skill and the guidance in the specification and the art. The Examiner in effect is asserting that to be definite, the claims must itemize each and every conceivable *in vivo* cleavable ester. It is respectfully submitted that there is no such requirement in the law or the rules of the US Patent and Trademark Office.

With respect to enablement, the Examiner asserts that it would involve undue experimentation for the chemist skilled in this art to make other esters and determine whether they are *in vivo* cleavable. However, as the Examiner must be aware, the test of "undue experimentation" is the nature of the experimentation required, not necessarily the amount. Here, considering the skill and knowledge already in the art and the guidance provided by the

[1] It should be noted in passing that neither original claim 6 nor reformatted claim 6 includes the phrase "*in vivo* cleavable ester."

specification, no more than routine reaction chemistry and tests would be required to extend the list of esters beyond those noted in the specification – certainly not "undue experimentation" when properly construed.

Nevertheless, in order to expedite the progress of this application toward allowance (or toward appeal), all claims referring to "*in vivo* cleavable esters" have been amended to further define that such esters are formed on available carboxy or hydroxy groups. It is respectfully submitted that forming an ester on an available hydroxy or carboxy group is certainly not beyond the skill of the chemists in this art.

Prodrugs of structurally claimed compounds, including esters, which are metabolically hydrolyzed or cleaved to form the active, structurally defined compound, have been included in claims of United States patents for decades. The undersigned is unaware of any Board or Federal Circuit case which finds that such claims now violate paragraph 1 or 2 of section 112. The undersigned has asked the Examiner to cite the case law or written policy change whereby Examiners are authorized (or instructed) to now reject prodrug claims. However, nothing has been cited that would account for this relatively recent and drastic change in policy. Therefore, applicants and the undersigned remain of the view that the present composition claims should be allowable under the law, without need for the above amendments, and these amendments have been made solely for the purpose of expediency in an attempt to bring this application to allowance, without waiver of applicants' right to pursue the broader claims in a continuing application.

Section 112 Rejection of Method Claims

In a sincere effort to bring this application to allowance, applicants previously limited claim 12 from "cytokine" to "TNF," and added claim 13 separately reciting disease or medical conditions mediated by the production or effect of the interleukins IL-1, IL-6 or IL-8. However, amended and new claims 12 and 13 have been rejected as well. These grounds for rejection were exhaustively addressed in applicants' Amendment and Response of November 6, 2002 at pages 14 to 20, and again noted in Amendment and Response after final filed May 30, 2003 at pages 19-20, and are cross-referenced here rather than being repeated.

Claims of the "mediated by" format have been accepted and understood for years in U.S. patent claims, as previously noted, without Board or Federal Circuit objection, and it is unknown on what basis this form of claim has now come into disfavor. Clearly, such a claim format *per se* covers (and always has covered) the beneficial pharmacological action demonstrated by applicants' compounds, and it is not believed to be material that such a pharmacological action may later be found to be of benefit in the treatment of specific disease conditions which are not specifically recited in the specification, no less exhaustively itemized in the claims, as the Examiner now seems to be requiring. The undersigned (as well as other practitioners) are confused by the widely varying approach taken by different Examiners in this Group in recent months with respect to acceptable formats for method of treatment claims, despite clear precedent from prior practice and granted patents. The above amendment adding method claims 14-18, therefore, addresses the disclosed methods for using the claimed compounds in several different formats, each of which formats has routinely been allowed and issued in pharmaceutical patents in the past. It is respectfully

submitted that each of these claims is appropriate in format, fully enabled by the specification, and supported by the disclosure. Support for these new method claims is found throughout the specification, and particularly at pages 1 to 3 and 49 to 52, as well as in the biological assays beginning at the bottom of page 42.

Conclusion

Entry of the above amendments is believed to appropriate and is respectfully requested. All claims are now believed to be in condition for allowance, and reconsideration and withdrawal of all grounds for rejection, and allowance of all claims is respectfully requested in view of the above amendments and remarks.

Respectfully Submitted,
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